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# The role of magnetic resonance imaging in the diagnosis and management of prostate cancer

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## Background

- The diagnosis of prostate cancer has long been plagued by the absence of an imaging tool that reliably detects and localises significant tumours. Recent evidence suggests that multi-parametric MRI could improve the accuracy of diagnostic assessment in prostate cancer. This review serves as a background to a recent USANZ position statement. It aims to provide an overview of MRI techniques and to critically review the published literature on the clinical application of MRI in prostate cancer.

## Technical Aspects

- The combination of anatomical (T2-weighted) MRI with at least two of the three functional MRI parameters – which include diffusion-weighted imaging, dynamic contrast-enhanced imaging and spectroscopy – will detect greater than 90% of significant (moderate to high risk) tumours; however MRI is less reliable at detecting tumours that are small (<0.5 cc), low grade (Gleason score 6) or in the transitional zone. The higher anatomical resolution provided by 3-Tesla magnets and endorectal coils may improve the accuracy, particularly in primary tumour staging.

## Screening

- The use of mpMRI to determine which men with an elevated PSA should undergo biopsy is currently the subject of two large clinical trials in Australia. MRI should be used with caution in this setting and then only in centres with established uro-radiological expertise and quality control mechanisms in place. There is sufficient evidence to justify using MRI to determine the need for repeat biopsy and to guide areas in which to focus repeat biopsy.

## Image-Directed Biopsy

- MRI-directed biopsy is an exciting concept supported by promising early results, but none of the three proposed techniques have so far been proven superior to standard biopsy protocols. Further evidence of superior accuracy and core-efficiency over standard biopsy is required, before their costs and complexities in use can be justified.

## Treatment Selection and Planning

- When used for primary-tumour staging (T-staging), MRI has limited sensitivity for T3 disease, but its specificity of greater than 95% may be useful in men with intermediate-high risk disease to identify those with advanced T3 disease not suitable for nerve sparing or for surgery at all. MRI appears to be of value in planning dosimetry in men undergoing radiotherapy, and in guiding selection for and monitoring on active surveillance.

## Introduction

Prostate cancer (PCa) is the most common non-cutaneous cancer diagnosed and second most common cause of cancer death in Australian and New Zealand men. These countries have the highest incidence of prostate cancer in the world (104 per 100,000 men each year). The incidence is rising due to a high uptake rate of Prostate-Specific Antigen screening and increasing life expectancy, constituting a significant public health challenge [5]. Screening for prostate cancer is problematic and remains controversial, as discussed in current North American and European guidelines [1,4]. PSA has a poor specificity for significant cancer at acceptable sensitivity thresholds [6], such that at least 60–70% of initial biopsies in men with a raised PSA are negative, and up to 45% of all cancers diagnosed (based on figures from the USA) are low-risk [3]. DRE has poor sensitivity, limited specificity and high inter-observer variability [7,8,9]. Trans-rectal Ultrasound



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(TRUS) is unreliable, thus 10–14 core template TRUS-biopsy is the standard of care, despite sub-optimal sensitivity with 20% false-negatives and a 30–45% risk of pathological up-staging [10,11] or down-staging [12] in those in men classified as low risk who proceed to RP. Saturation and template mapping biopsies do not solve the problem due to increased costs, complications, over-detection rates and a small but significant risk of missing high grade cancer. A reliable imaging technique could reduce unnecessary biopsies, avoid false negative biopsies, reduce the number of cores required, improve selection of low risk men for surveillance, and improve selection and planning of therapy in intermediate to high risk men.

This article – which serves as a background to a recently published USANZ position statement – aims to provide an overview of multi-parametric MRI, to review evidence regarding its accuracy and to discuss its emerging role in three challenging areas of prostate cancer management: early detection, active surveillance and treatment planning.

**Criteria used for literature review:** Relevant manuscripts were found through searches of Medline, Embase and Science Direct when including combinations of, but not exclusively, the terms "prostate", "neoplasm", "diagnosis", "early detection", "screening", "biopsy", "staging", "therapy", "active surveillance", "nerve sparing", "surgery", "radiotherapy", "focal therapy", "Magnetic Resonance Imaging", "Magnetic Resonance Spectroscopy", "diffusion-weighted MRI", "Multiparametric MRI", "dynamic contrast-enhanced MRI", and "guidelines". All abstracts were reviewed and full-text articles obtained where possible. References to and from obtained articles were searched to identify further relevant articles.

## Overview of Multi-Parametric MRI

Unlike other solid tumours, prostate tumours often elude imaging modalities such as computed tomography and grey-scale ultrasound. MRI is a non-invasive method of demonstrating anatomy and pathology based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radio waves that can be received then reconstructed into 3-D images. Prostate MRI using T1- and T2-weighted imaging was trialled in the 1980s, but at the time it lacked the adequate sensitivity and specificity to justify routine use [13]. Since then, technical improvements and the addition of functional parameters (diffusion-weighted, dynamic contrast-enhanced and spectroscopic imaging) to purely anatomic (T1/2-weighted) imaging have improved its accuracy. Recent reviews have suggested that contemporary multi-parametric MRI (mpMRI, Fig. 1) reliably detects clinically significant prostate tumours and provides critical information regarding tumour location, volume, grade and stage [14,15].

### T2-Weighted Imaging

T2-Weighted Imaging (T2WI) is the foundation of mpMRI because it provides high-resolution images that clearly define prostate anatomy. The normal peripheral zone is characterised by an intermediate to high signal intensity due to its high water content, while a focus of cancer exhibits low signal due to its dense cellularity. Low signal on T2WI in the peripheral zone is not specific for cancer, with differential diagnoses including chronic prostatitis, atrophy and post-biopsy effects (scarring or haemorrhage). Analysis of the size, shape, homogeneity and focality of low signal is used by specialists in prostate MRI to improve the specificity of T2WI for PCa [25–27], while T1-weighted imaging is highly accurate at differentiating post-biopsy haemorrhage from tumour. In the transitional and anterior zones, the baseline T2 signal is lower and focal hypo-intense nodules caused by BPH are common; this reduced the detection accuracy of T2WI for cancer in these zones. T2WI alone is estimated to have a sensitivity of 48–88%, specificity of 44–81% and Area Under the Receiver Operating Curve (AUC-ROC) of 0.68–0.81 compared to radical prostatectomy [17–21]. The wide variation in these accuracy estimates is in part due to exclusion of transitional/anterior cancers and insignificant cancers from the analysis in some studies.

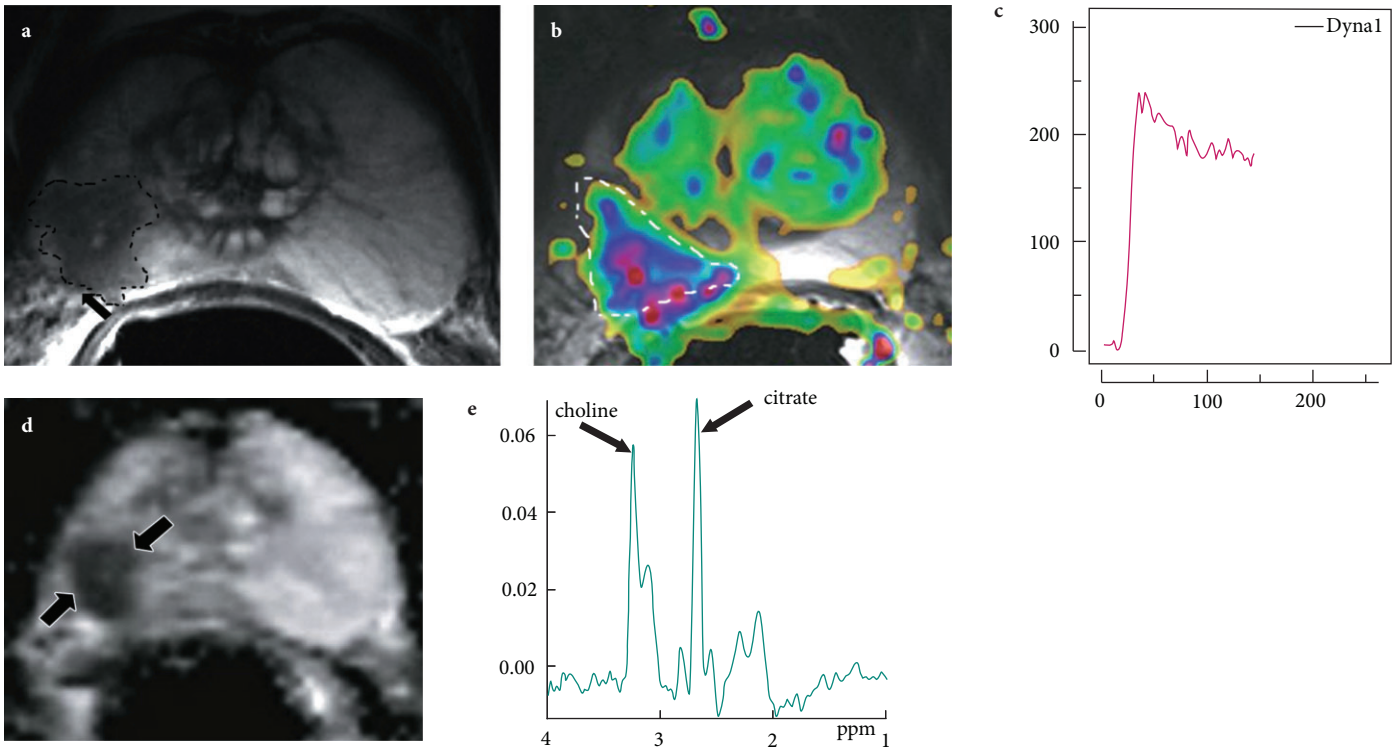
### Diffusion Weighted Imaging

Diffusion-weighted imaging (DWI) measures the diffusion of water molecules through tissue in the presence of a strong magnetic field and radiofrequency pulses. The diffusion of water varies between normal tissue types as well as between type of pathological process. Prostate cancer exhibits a reduced diffusion of water compared to normal prostate tissue due to its tightly packed cells with a relative decrease in water content, and due to the disruption of interstitial spaces and planes through which water normally diffuses. Apparent diffusion coefficient (ADC) maps of the prostate are then derived, which demonstrate tumour as an area of focal low signal relative to the surrounding prostate. DWI provides a strong and easily visible contrast between tumour and benign tissue with short acquisition times, however the spatial resolution is poor. Thus it must be combined with T2WI. A number of studies have shown that DWI combined with T2WI has superior diagnostic accuracy to T2WI alone, with sensitivity and specificity of 85–90% and ROC-AUC of 0.80–0.90 when compared to radical prostatectomy findings Table 2 [22,29–31].

### Dynamic Contrast Enhanced Imaging

Dynamic contrast-enhanced imaging (DCEI) comprises a bolus of intravenous gadolinium contrast, followed by a series of rapid sequential scans at short time intervals. Each scan demonstrates a map of perfusion in each spatial region of the

**Fig. 1** Images of prostate cancer in the right postero-lateral peripheral zone as seen on various parameters of mpMRI: (a) focal low signal (dark area) on T2WI; (b) focal early and intense contrast enhancement on DCEI; (c) classic type 3 DCEI curve showing early, intense enhancement followed by rapid washout; (d) focal reduced diffusion (dark area) on DWI; (e) increased peak choline: citrate ratio on MRS (Adapted from Hoeks C et al, Radiology 2011, with permission from RSNA).




prostate at a single point in time; the perfusion of a region of interest (i.e. an area of suspicion on T2WI or DWI) can be plotted graphically against time to create a perfusion vs time curve. Three types of curve have been defined [32,33]:

- High-grade tumour is typified a focal type 3 curve, which is characterised by early and intense contrast enhancement followed by rapid washout;
- BPH and prostatitis are typified by a diffuse or multi-focal type 2 curve, which is characterised early and intense enhancement followed by slow washout of contrast; sparse/multi-focal low grade tumour can also display this pattern of enhancement;
- Normal tissue displays a diffuse type 1 curve, in which average enhancement and washout is seen throughout the gland.

DCEI combined with T2WI has been found to have a sensitivity and specificity of up to 90–95% and ROC-AUC of 0.90 (compared to radical prostatectomy) for significant cancer [23,34]. Its accuracy is impaired by BPH and prostatitis, which are the most common differential diagnoses in men with a raised PSA. It has been shown in at least one study to add value in detection and localisation of tumours after a previous negative biopsy [35].

## Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) is a functional technique indirectly measures metabolite levels in the prostate by region of interest. Cellular concentrations of choline and creatine increase in prostate tumour and correspond to the volume and grade of the tumour, while the concentration of citrate decreases as tumour volume and grade increase. The combination of MRS and T2WI detected prostate tumours with a specificity of 79–93% and sensitivity of 72–89%[16,19] compared to radical prostatectomy, although no incremental benefit of adding MRS to T2WI was seen in a prospective trial of 110 men (ROC-AUC 0.60 vs 0.58 respectively)[36]. In detecting tumours of >3 mm diameter in the peripheral zone, MRS had a high specificity of 98% (compared to 83% for T2WI and 94% DCEI) but at the cost of a poor sensitivity of 53% when used alone (compared to 94% for T2WI and 56% for DCEI).

## MRI Correlation with Tumour Volume and Grade

The ability of MRI to selectively detect higher grade and volume tumours is important in that it could reduce over-detection of insignificant cancer if used to direct biopsy or select men to biopsy, and could be used in active

**Table 1** Summary of recommendations regarding the role of MRI in Prostate Cancer from commonly used Guidelines.

| Guidelines | Overall Recommendation | Early detection (screening) | Localisation and targeted biopsies | Staging & Treatment Planning | Active Surveillance/Focal therapy | Recurrence post treatment |
|---|---|---|---|---|---|---|
| **European Association Urology [1] 2011** | MRI is now of a high technical standard, but not sufficiently reliable to make use mandatory | No comment | If suspicion for PCa persists despite negative biopsies, MRI may be used to investigate a possible anterior PCa, followed by TRUS/ MRI-guided biopsy of the suspicious area. | MRI demonstrates higher accuracy than DRE, TRUS & CT for the assessment of uni/bilobar disease (T2), ECE/ SVI (T3), and invasion of adjacent organs (T4)<br>Adding MRS increases accuracy & reduces inter-observer variability in the evaluation of ECE | No comment | Pelvic MRI or CT may be used to detect metastases post-treatment, particularly when PSA > 20 |
| **European Society of Urogenital Radiology [2] 2012** | mp-MRI should be an integral part of prostate cancer diagnosis and treatment | No comment | In men where repeat biopsy is indicated, MRI-directed TRUS biopsy or real-time MRI-guided biopsy must be used routinely | Surgical planning: MRI helps detect ECE to plan nerve-sparing & continence-preserving surgery<br>Nodal staging: Lymph node staging using MRI is unreliable, and should only be done where probability is >40%<br>Primary radiotherapy: MRI may help direct radiotherapy | MRI before enrolment in AS allows detection of adverse prognostic features such as high tumour volume/ grade, particularly in anterior and apical tumours<br>MRI can be used to direct further biopsy for more accurate grading and volume assessment of tumour | MRI can be considered to be a tool to evaluate the prostatic fossa in patients with low PSA recurrence (PSA 0.2–2 ng/mL) |
| **National Comprehensive Cancer Network (North America)[3,4]** | Not accepted as essential in the workup of all patients. Optional in specific instances | No comment | Multi-parametric MRI can aid in cancer detection in patients with persistent PSA elevation but negative TRUS-biopsy | MRI has yet to be accepted as essential in tumour staging<br>MRI is indicated for nodal staging if cT3-4, PSA >20–25 or if the nomogram-derived probability of nodal metastases is >20% | No comment | No comment |

**Table 2** The reported accuracy of multi-parametric MRI in PCa detection from selected studies.

| 1st Auth & Public'n Yr | Type of MRI | Methods | Standard of reference | Outcome measure | Results |
|---|---|---|---|---|---|
| **Villeirs 2011 [16]** | T2 & MRS 1.5T | Retrospective 365 men, mean PSA 12, 40% MRI before biopsy, 60% known PCa before MRI 21 mo f/up in –ve Bx cases | 6–14 core TRUS biopsy | Accuracy – Overall – Gleason >/= 4+3 | PPV 94%, NPV 67%, Accuracy 80% Sens 93%, Spec 93%, NPV 98% |
| **Futterer 2006 [17]** | T2, DCE & MRS 1.5T | Prospective 34 men, Known PCa, median Biopsy Gleason 6 | Radical Prostatectomy | Accuracy – Overall – Tumours > 0.5 cc | T2 69%, T2+DCE n/a, T2+MRS 78% T2 71%, T2+DCE 90%, T2+MRS 85% |
| **Kim 2005 [18]** | T2 & DCE 1.5T | 53 men, known PCa, mean Biopsy Gleason 7 | Radical Prostatectomy | Accuracy: – Overall – Peripheral zone – Transitional zone | T2 62%, T2 + DCE 88% T2 63%, T2 + DCE 97% T2 60%, T2 + DCE 72% |
| **Tanimoto 2007 [19]** | T2 & DWI 1.5T | 83 men, mean PSA 19, MRI then biopsy, 53% + for PCa | Standard TRUS biopsy | Accuracy (AUC) | T2 0.71 T2 + DWI 0.91 T2 + DWI + DCE 0.97 |
| **Cheikh 2009 [20]** | T2 &DCE 1.5T | 93 men, mean PSA 9.6, previous negative biopsy, MRI then repeat biopsy | 12 core TRUS biopsy + cognitive MRI-directed cores | Sensitivity Specificity | T2 48%, DCE 83%, T2+DCE 48% T2 44%, DCE 20%, T2+DCE 51% |
| **Chen 2008 [21]** | T2, DWI & MRS 1.5T | 42 men, MRI then biopsy, 36% + for PCa | Standard TRUS biopsy | Sensitivity Specificity AUC-ROC | T2 88%, DWI 82%, MRS 84%, All 96% T2 67%, DWI 82%, MRS 98%, All 97% T2 0.85, DWI 0.86, MRS 0.96, All 0.98 |
| **Haider 2007 [22]** | T2 & DWI 1.5T | Prospective 49 men, Known PCa, MRI then RP | Radical Prostatectomy | For tumours >4 mm: – Sensitivity – Specificity | T2 54%, T2 + DWI 81% T2 91%, T2 + DWI 84% |
| **Puech 2009 [23]** | T2 & DCE 1.5T | Retrospective 83 men, known PCa, MRI then RP | Radical Prostatectomy (analysed by octants) | Accuracy – Overall – Tumours > 0.5 cc – Tumours with >10% Gleason 4/5 | Sensitivity 32%, Specificity 95% Sens 86%, Spec 94%, ROC 0.87 Sensitivity 81%, specificity 82% |
| **Mazaheri 2008 [24]** | DWI & MRS 1.5T | Retrospective 38 men, Known PCa, MRI then RP | Radical Prostatectomy | ROC-AUC for PZ tumours >0.1 cc | DWI 0.81 MRS 0.74 DWI + MRS 0.85 |

surveillance for selection and monitoring. T2WI, DWI and MRS have all been shown to be useful for quantitative analysis that can be used to estimate Gleason grade and volume:

- T2WI has been shown in one recent study to selectively and reliably detected tumour foci that were Gleason >/= 7 & had a volume > 0.5 $cm^3$ (ROC-AUC ~ 0.8), or foci that were Gleason 6 & had a volume > 1 $cm^3$ (ROC-AUC ~ 0.9) [37]. Three studies have found that the intensity of T2 signal correlates with Gleason score [38,39], even after adjusting for size in a multivariate analysis [40].
- DWI uses ADCs as a quantitative measure, which correlate closely with Gleason score, volume and risk-category; this leads to increased specificity of DWI for clinically significant tumours, as evidenced by seven recent studies [24,41–47] that analysed DWI findings against prostatectomy specimens.
- MRS has been shown to correlate strongly with Gleason score in four studies that analysed MRS against prostatectomy findings [16,24,48,49]. In one study of 365 men who underwent combined T2WI + MRS then initial biopsy, MRI selectively detected Gleason >/= 7 tumours with a sensitivity of 93% and specificity of 93%, compared to a sensitivity of only 68% for Gleason 6 tumours (with predominately larger volume Gleason 6 tumours detected over smaller tumours) [16].

## Selection of MRI Magnet Strength and Coil Type

The use of an endo-rectal coil (ERC) improves anatomic definition at the cost of significant patient discomfort, time and cost; this may be justified when MRI is performed specifically for T-staging men with PCa but not when performed for initial detection or surveillance, in which case a pelvic phased array (PPA) coil may be adequate [2]. A number of small, retrospective studies have suggested that adding an ERC improves accuracy of T-staging at 1.5T [26,50–55], however other studies at 1.5T have contradicted this finding [56].

Advances in MRI technology have led to the availability of magnets with up to 3-Tesla (3T) field-strength, which reduce acquisition times and provide superior anatomical definition due to a two-fold increase in the signal-to-noise ratio (SNR). Use of 3T MRI with no ERC provided equivalent accuracy in staging to a 1.5T MRI with an ERC in one study of 151 men, however the sensitivity with both techniques for T3a disease was disturbingly low at 31% and 33% respectively [57]. Sensitivity for T3 disease in staging could perhaps be

improved by using both a 3T magnet and an ERC, as suggested by one small study of 46 men that found a sensitivity of 77% for an ERC versus only 7% for no ERC, with all patients scanned at 3T [58].

## Determining the Optimal Combination of MRI Parameters

Individually, the functional MRI techniques (MRSI, DWI, and DCE) add value to conventional anatomic (T2WI) MRI in detection, localisation, grading and staging of prostate cancer PCa (Table 3), as discussed above and in a number of recent reviews [59–63]. The optimal combination of parameters, magnets and coils will provide the best balance of maximal accuracy, minimal invasiveness, shortest duration and lowest cost. The optimal combination varies according to the indication, hence different protocols are recommended for detection, tumour staging and node-bone staging in the European Society of Uro-Radiology (ESUR) guidelines [2]. For initial detection and localisation, the combination of T2WI, DWI and DCEI without an ER coil at either 1.5T or 3T provides the best balance of accuracy, comfort, duration and cost. Use of 3T and an endorectal coil may be unnecessary except in T-staging, and MRS appears unnecessary except perhaps in staging and/ or active surveillance [16,62,64,65].

## Determining the Optimal Timing of MRI after Biopsy

Biopsy causes haemorrhage, inflammation, infarction and fibrosis in the prostate gland. This causes early abnormalities that may persist for several months and even permanent abnormalities (infarcts and scarring), all of which can mimic tumour on MRI. Capsular irregularity, thickening and retraction after biopsy mimic extra-prostatic extension. Most radiologists therefore recommend an interval of at least 6–8 weeks between biopsy and MRI, to minimise haemorrhage and prostatitis. When an MRI is performed soon after biopsy, addition of T1WI is recommended to differentiate tumour from post-biopsy haemorrhage: haemorrhage will appear as pathognomonic high signal intensity on T1WI [66]. Two studies found that quantitative T2WI and DWI reliably differentiated tumour from haemorrhage [67,68], suggesting delay may be unnecessary.

## Standardisation of Reporting Using the PIRADS System

The PI-RADS system (Prostate Imaging – Reporting and Data System) is a standardised reporting tool developed by the ESUR and proposed for use in reporting prostate MRI. A score is designated for each parameter according to a 5-point scale (i.e. the presence of clinically significant cancer is: 1= 'extremely unlikely', 2 = 'unlikely', 3 = 'equivocal', 4 = 'likely', 5 = 'extremely likely') based on objective and/ or quantitative findings. A score is given for each parameter within each 'region of interest' (ROI), and an overall score representing the impression of the radiologist may be given for each area of interest as well as a score for the prostate as a whole (see example below, Table 4). MRI images of the ROI on each parameter, and a topographic diagram showing the exact location of the lesion, assist the clinician who may use the MRI report to target biopsy or treatment to that area.

Each ROI is scored on based on a combination of qualitative features and quantitative measures, such as those discussed above under each parameter. A detailed description of the criteria used in the PI-RADS system is beyond the scope of this article, but can be found elsewhere [2]. The theoretical advantage of using such a system is that it improves

**Table 3** Types of MR sequence and implications for PCa imaging (adapted from Raz et al, Nat Rev Urol 2010 [28], with permission from Nature Publishing Group).

| MR sequence | Technical details | Implications for prostate cancer imaging |
|---|---|---|
| **T1-weighted imaging** | Gradient echo sequence, with short echo and repetition times<br>Very fast, allowing the collection of high resolution 3D data<br>Can be used with contrast agents. | Prostate gland appears homogeneous<br>Detects haemorrhage secondary to prostate biopsy as hyper-intense regions |
| **T2-weighted imaging** | Spin echo sequence, with long echo and repetition times.<br>Less susceptible to variation in the magnetic field<br>Sensitive to water content | High anatomical resolution<br>Tumours appear as round or ill defined low intensity foci<br>Extra capsular extension can be directly observed |
| **Spectroscopy** | MR signal produces a spectrum of resonances corresponding to different molecular arrangements of the "excited" isotope<br>This allows the relative concentrations of various intracellular molecules to be quantified and mapped in 3-dimensions | In tumour cells the production of citrate is reduced whereas choline is increased<br>Areas of tumour are therefore characterised by a focally increased choline: citrate ratio |
| **Dynamic contrast-enhanced imaging** | Gadolinium diffuses from the vascular space to the extracellular space and then leaks slowly back into the vascular space<br>The rate of forward and backward leakage, and the fractional volume of the extracellular space can be calculated | Tumours show early enhancement and washout of gadolinium<br>Calculated measures correlate with tumour grade and volume<br>Prostatitis and BPH also show increased enhancement but with different patterns to tumour on curve analysis |
| **Diffusion-weighted imaging** | Water molecules move according to Brownian Motion. In tissue, the diffusion may be in one direction within a magnetic field<br>The signal emitted is proportional to the distance water travels. Longer distance = higher apparent diffusion coefficient (ADC) | ADCs correlate with micro-vessel density and cellularity: micro-vessel perfusion causes the "fast" diffusion component & extra-/ intra-cellular water diffusion causes the "slow" component.<br>Reduced water diffusion due to disrupted tissue planes and higher cellular density is characteristic of a tumour focus |

**Table 4** Excerpt from an MRI report using the PI-RADS system.

| Location on MRI | T2WI | DCEI | DWI | Overall | Overall for whole prostate |
|---|---|---|---|---|---|
| Left anterior apex | 4 | 4 | 5 | 4 | 4 |
| Right lateral mid | 3 | 2 | 2 | 2 | |

*Two regions of interest were identified in this report – a focal abnormality 'likely' to be significant cancer (overall PI-RADS score 4 out of 5) is identified, as well as a focal abnormality 'unlikely' to be significant cancer (overall PI-RADS score 2 out of 5); an overall score for the entire prostate was also provided.*

consistency and objectivity in reporting and improves communication between the radiologist and clinician. The criteria are based on published literature and expert opinion and the BI-RADS system used successfully in MRI for breast cancer detection, but it has not yet been prospectively validated as a reporting tool and there is a lack of international consensus on the reporting of prostate MRI [69].

## MRI-Guided Prostate Biopsy

The current standard of care for initial prostate biopsy is a 12–14 core TRUS-guided biopsy, with a detection rate for prostate cancer of 27–44%[70–72]. Some urologists perform an initial saturation biopsy (>/=20 cores) in the hope of increasing the sensitivity and risk-stratification, but studies show minimal improvement in the detection rate between standard and saturation protocols for initial biopsy [73–75]. Template mapping biopsies with a median of 40–69 cores have been shown to have a variable but generally higher detection rate (up to 76% for initial biopsy in one study, but as low as 11% in another study) and more accurate risk stratification, but take much longer and have significantly higher surgical and pathology costs, as well as a higher complication rate (8–30%), a higher over-diagnosis rate of insignificant cancer and the potential to compromise of nerve sparing surgery [76–79].

MRI-targeted biopsy has been proposed as a way to improve detection rates and accuracy of risk stratification, as well as reducing the number of cores. A recent systematic review [80] concluded that MRI-guided biopsy detects significant prostate cancer in an equivalent or higher number of men to standard biopsy, using fewer cores with less complications and less diagnosis of insignificant cancer. However, due to variability in study methodology, the recommendations could not be definitive, with the authors citing the need for a multicentre, prospective trial of targeted biopsies. Three MRI-directed biopsy techniques have been proposed. The optimal technique of MRI-directed biopsy remains to be determined, and each will be discussed in turn.

1) MRI-informed, free-hand/ cognitive TRUS-guided biopsy

The simplest technique to biopsy an MRI-derived target is to review the images, then manually correlate the MRI-suspicious region with real-time TRUS images based on landmarks such as contours and calcifications, then attempt 'free-hand' to perform a TRUS-guided biopsy of the MRI-suspicious region. The advantage of this approach is that it doesn't require any specialised, expensive biopsy equipment, change in biopsy technique or direct access to an MRI machine for the urologist, and it can be easily incorporated into existing office or operating theatre-based biopsies. The disadvantage is the large potential margin of error, with no guarantee that the manual biopsy will sample the MRI-suspicious region, especially given the deformation of the prostate due to the transrectal probe and firing of the biopsy gun.

Three studies have reported on this technique. The first [81] prospective study performed T2WI & DCEI in 555 men with high PSA (median 6.75) or abnormal DRE then a 10-core TRUS-biopsy plus freehand/ cognitive TRUS-biopsy of MRI suspicious regions. 63% of men had a positive MRI; sensitivity, specificity and accuracy of MRI for significant cancer was 95%, 100% and 98% respectively, compared to 95%, 83% and 88% respectively for standard TRUS-biopsy (using combined biopsy findings as the reference). If only targeted cores had been performed instead of standard TRUS biopsy, 37% of biopsies would have been avoided, an equal number significant cancers would have been missed (5%), a mean of 3.8 instead of 10 cores would have been required, 13% of insignificant cancers would not have been over-detected, and detected cancers would have had more accurate grading (16% more Gleason 4/5 tumours detected) and volume assessment. The second study was a randomised controlled trial [82]: 85 men with abnormal PSA/ DRE and no previous biopsy were allocated to either MRI (T2WI, DWI & DCEI) then TRUS standard 10–12 core biopsy plus freehand MRI-directed biopsy, or standard TRUS biopsy alone. The MRI group had a three-fold higher detection rate (29.5% vs 9.8%) with an OR of 3.9 (95% CI 1.1–13.1, $p = 0.03$); the MRI group also had a four-fold higher positive core rate (9.9% vs 2.5%) with an OR of 4.2 (95% CI 2.2–8.1, $p < 0.01$); this suggests more accurate detection and risk stratification in those undergoing MRI before biopsy, although the detection rate of only 9.8% in the control group of this Korean study was lower than rates in Western countries, which may limit generalisation to other populations.

In the largest and most recent prospective study, 182 consecutive men with an MRI-suspicious lesion underwent transperineal free-hand MRI-directed biopsy (MRI-Bx, median 5 cores), followed by a systematic template transperineal mapping biopsy (TM-Bx, median 30 cores); 43% were biopsy naïve, 18% had a previous negative biopsy, and 40% had known prostate cancer. Clinically significant prostate cancer (Gleason >/=7 or max core length of PCa >/= 4 mm) was detected with a similar rate for both techniques (57% for MRI-Bx alone vs 62% for TM-Bx alone, $p = 0.174$), however MRI-Bx had a much higher proportion of positive cores (38% vs 14%) and a significantly lower rate of over-diagnosis of

insignificant cancer (9% vs 17%, p = 0.024), together with avoidance of the high complication rate of TM-Bx [83].

2) In-gantry (real-time) MRI-guided biopsy

This is the most complex – but perhaps the most accurate – technique for MRI-guided biopsy. In men with a suspicious area on diagnostic MRI, an MRI-compatible biopsy device (on a table-mounted platform that allows calibrated fine movements of the biopsy gun in all planes) is inserted with the patient in the prone position (under local anaesthetic +/- sedation) and repeated T2W-MRIs are performed until the estimated biopsy trajectory is centred on the MRI-suspicious region. The biopsy needle is then deployed and the position of the biopsy checked by taking a scan with the needle in situ. More biopsies are taken if the needle does not sample the desired region. Sampling of the MRI-suspicious region is guaranteed, but disadvantages include a long total procedure time of 1–2 hours (although the procedure time may be reduced to around 30 minutes after a learning curve of 100–150 cases), high costs and resource intensiveness (although these may be offset by the avoidance of an anaesthetic and day surgery unit hospitalisation), difficulty gaining prolonged access to the MRI machine due to heavily booked schedules of most MRI machines, inability to integrate with routine operating lists/ office biopsies, inability to combine with a standard template biopsy and patient discomfort.

One study reported on 71 consecutive men with at least two negative TRUS-biopsies who then underwent mpMRI: 70 had an MRI-suspicious region and 68 underwent in-gantry MRI-guided biopsy: the cancer detection rate was 59% of which 93% were clinically significant cancers; MRI-guided biopsy was compared to a matched reference group who underwent repeat TRUS-biopsy, and the authors found that MRI-guided biopsy detected significantly more tumours than standard repeat TRUS-biopsy (22% for second and 15% for third TRUS-biopsy) [84]. In a separate study by the same research group, 34 men underwent mpMRI then MR-guided biopsy of DWI-derived targets followed by RP; the biopsy-to-prostatectomy Gleason upgrading rate was compared with that of a matched cohort of 64 men who underwent standard TRUS 10core biopsy followed by prostatectomy. The authors reported that Gleason grade on DWI-guided biopsy accurately predicted the Gleason grade at RP in 88% of cases, whereas Gleason grade on standard 10-core biopsy predicted the Gleason grade at RP in only 55% of cases [85]. This supports the hypothesis that MRI-guided biopsy more accurately risk-stratifies Pca than standard biopsy. The largest series to date reported a detection rate of 41% in 96 men, however their study has been criticised for only using single parameter T2WI at 1–1.5T to identify MRI suspicious regions for biopsy, and they noted that 18% of men with a negative MR-biopsy were diagnosed subsequently with Pca at a median of 1.7 years [86].

3) MRI-TRUS Fusion-guided biopsy

This technique is really a hybrid or compromise between the two techniques above. The MRI images are downloaded onto the ultrasound machine via specialised software, then ultrasound images are acquired (via a quick axial TRUS from apex to base), then the software 'fuses' the MRI onto the corresponding US images; co-ordinates for the floor- or table-mounted stepper/ grid biopsy apparatus are then provided by the software, in order to guide the biopsy needle to the MRI-suspicious region, which is also highlighted on the screen following co-registration, to facilitate real-time TRUS-guided biopsy. The advantages and disadvantages of MRI-TRUS fusion lie between the two techniques above; fairly accurate sampling of the region of interest is achieved, although slight deformations of the prostate due to the TRUS probe and biopsy gun are not accounted for with existing technology. Studies which have measured the average distance between desired and actual biopsy location found it to be minimal at 1.7–2.4 mm [87,88], which is an acceptable margin of error that may be overcome by taking 2–3 cores. The overall cost lies between that of the other two techniques, the learning curve is fairly short, the technique can easily be incorporated into existing operating lists and combined with standard template biopsy, operative time is only increased by 10 minutes at most when combined with standard template biopsy, and in fact the operative time may be even be reduced if only MRI-directed biopsies were taken.

There are three published reports on MRI-TRUS fusion biopsy. The first reported on 101 men, of whom around one third underwent initial biopsy, one third underwent repeat biopsy and one third underwent re-staging biopsy for known PCa. They performed T2WI, DWI, DCEI and MRS at 3T with an ER coil then a 12-core TRUS biopsy plus fusion biopsy of an average of 2.6 MRI-derived targets. They reported that fusion + standard biopsy with a mean of 18 cores (12 standard + 6 fusion) had a high detection rate of 55%, with each technique alone having an equal sensitivity of 82% for PCa compared to the combined technique. Fusion biopsy thus detected PCa at the same sensitivity but required only half the number of cores [89].

The second study reported on 101 men of whom 43% were undergoing initial biopsy, 46% repeat biopsy and 10% surveillance biopsy. They performed T2WI, DWI, DCEI and MRS at 3T and then a saturation TRUS biopsy (median 20-cores) + additional fusion cores (median 4-cores). They reported a high detection rate of 67% in initial biopsy and 45% in repeat biopsy. 25% of fusion-directed cores were positive compared with only 9% of saturation cores. 96% of

highly suspicious MRI areas were positive for PCa, and 71% of moderately to highly suspicious areas were positive for PCa, however 35% of men whose MRI was not suspicious for PCa were found to have PCa on biopsy, giving an overall MRI to biopsy correlation of only 69% [87].

The third study used a fusion platform to perform a standard 8-core transrectal biopsy plus an MR-US fusion biopsy in 85 men with a rising PSA, previously negative 8-core TRUS biopsy and a positive MRI (T2WI + DCEI + DWI). 61% had cancer (defined as positive standard and/ or fusion biopsy) of whom 35% had PCa detected only by fusion biopsy, compared to 14% who had PCa detected only by standard biopsy. Unfortunately, all three studies failed to report the pathological characteristics or risk classification of detected tumours, preventing assessment of whether fusion selectively detected significant PCa's over insignificant PCa's when compared to standard biopsy [90].

## The Clinical Application of mpMRI – Potential Roles

### mpMRI to Guide Patient Selection for Initial Biopsy

Multi-parametric MRI appears to be able to exclude clinically significant cancer with a negative predictive value and specificity of around 90–95%. Therefore MRI has the potential to be used as a 'second-line screening' tool. Men with a mildly elevated PSA, normal DRE and no family history – whom would otherwise undergo biopsy but in whom mpMRI is normal – could be offered deferral of biopsy in the first instance, in favour of ongoing PSA and DRE monitoring. Those in whom the MRI detects a region of intermediate or high suspicion, on the other hand, would undergo a standard 6–16 core biopsy plus additional MRI-directed cores. Potential benefits of incorporating mpMRI into screening algorithms include:

- improved sensitivity of biopsy for intermediate to high risk cancer;
- more accurate assessment of tumour grade and volume;
- reduced over-detection of low risk cancer if used to select and guide biopsy;
- avoidance of biopsies in low risk men with a normal MRI;
- reduction in the number of cores per biopsy;
- exclusion of high risk PCa in men with high PSA but limited life expectancy/ multiple negative biopsies

There are no published studies trialling mpMRI to select which men should undergo biopsy, and to perform such studies may be unethical until a larger body of evidence suggests that mpMRI has an equal or greater sensitivity and superior specificity for significant cancer compared with standard biopsy, in a screening population. We cant ethically perform radical prostatectomy in men with a negative biopsy, therefore one way to answer this question in a screening cohort is to compare mpMRI with a template biopsy of 30 cores plus 0–4 MRI-directed cores, then follow up those in whom biopsy is negative for 3–5 years.

### mpMRI in Selecting Men for Repeat Biopsy

In the common clinical scenario of men with a rising PSA and one or more previously negative standard TRUS biopsies, mpMRI has been shown to be a particularly valuable investigation, because it often localises an area of suspicion in the 30% of men with PCa whose tumour originates in the anterior or transitional zone [91], where cancer is often missed by standard TRUS biopsy protocols. One study [92] reported on a case series of men with previous negative biopsy or on active surveillance, in whom mpMRI had a PPV of 87% for anterior cancer, with 44% of cancers being Gleason >/=7. Another study analysed combined data from 215 men across six prospective studies of MRI prior to repeat biopsy for rising PSA, and found that – in those who had both standard and MRI-directed cores taken – that 54% had PCa detected purely by MRI-directed cores (i.e. standard cores missed the cancer in 54% of cases)[15]. As a result of this and other, mpMRI is now recommended according to EAU, NCCN and ESUR guidelines for men with a rising PSA and suspicion of cancer despite multiple negative biopsies (see Table 1).

### mpMRI in Active Surveillance

Men with newly diagnosed PCa are stratified into risk categories from 'very low' to 'high' according to criteria such as those proposed by Epstein or the NCCN, while nomograms such as those of Kattan and colleagues [93,94] are used to guide treatment decisions and estimate prognosis. Our ability to reliably discriminate between insignificant and life-threatening prostate cancer at the time of diagnosis remains limited, which often leads to over-treatment: 15–30% of all screen-detected cancers that are treated with radical prostatectomy are estimated to be insignificant on histopathology [6,95]. As a result of over-treatment, 48 men needed to be treated for PCa in order to save one life in the recent ERSPC trial [96]. A recent global review of autopsy studies showed that as many as 40% of all men over 50 have low risk prostate cancer [97].

One strategy used to reduce over-treatment is 'active surveillance' (AS) for selected men with low-risk PCa and a life expectancy greater than 10 years, since treatment of this group may not confer a net benefit in terms of survival or quality of life (QOL). The major limitation of active surveillance is that enrolment and monitoring protocols are subject to significant error: a significant proportion (30–50%) of men thought to be appropriate for surveillance on initial biopsy are re-classified as moderate-high risk at their first or second surveillance biopsy [98,99]; furthermore,

20–30% of men who are eligible for active surveillance but elect primary radical prostatectomy are found to have unfavourable (Gleason >/=7 or pT3) disease at prostatectomy [100].

Multi-parametric MRI may be a valuable tool in AS due to its high negative predictive value for intermediate-high risk PCa. Performed 6–8 weeks after diagnosis (to minimise post-biopsy artifact), it may identify most men with a focus of significant cancer that was missed on diagnostic biopsy. These men could either undergo early repeat biopsy of the MRI-suspicious region or proceed directly to definitive treatment if the MRI findings were highly specific for cancer and the patient preferred treatment over repeat biopsy. The following studies support the incorporation of MRI into surveillance protocols:

- In a cohort of 388 consecutive men with low risk PCa on initial biopsy who underwent MRI followed by initial surveillance/ confirmatory biopsy within 12 months, a negative MRI (score of 1–2 out of 5) had a 98% specificity and negative predictive value for ruling out Gleason upgrading, while a positive MRI (score of 5 out of 5) was 93% sensitive for Gleason upgrading (20% of the cohort showed Gleason upgrading at first surveillance biopsy) [101].
- In a cohort of 50 men who underwent T2WI + DWI at enrolment onto AS and then again at 1–3 years, a decrease in ADC of >10% was predictive of progression (Sens 93%, Spec 40%, AUC = 0.68, $p < 0.05$)[42]. In a related report on 82 men who underwent T2WI + DWI at enrolment onto AS, ADC was a highly significant predictor of adverse findings at surveillance biopsy (HR 1.3, $p < 0.001$, AUC 0.70) and progression requiring radical treatment (HR 1.5, $p < 0.001$, AUC 0.83) [102]
- In a cohort of 60 men who were enrolled on AS and had mpMRI then repeat biopsy within a year, MRI predicted risk-upgrading with a PPV of 83% and NPV of 81% [103].
- In a case series of 66 men who had MRI then repeat biopsy within 3 months of AS enrolment, 27% of men had suspicion of ECE on MRI, 39% of whom were risk-upgraded on repeat biopsy; none of the 73% with a normal MRI were risk-upgraded at repeat biopsy [104].
- In a case series of 114 men who had T2WI + MRS at enrolment onto AS, those with a suspicious lesion on T2WI had a high risk of Gleason up-grading at surveillance biopsy (HR 4, 95%CI 1.1–14.9) compared to those with a normal MRI. MRS, however, was not a significant predictor of progression [105].

Three studies, however, failed to show a benefit of MRI in AS:

- In 96 low-risk men who underwent T2WI at 1.5T then RP, MRI failed to predict unfavourable disease at RP (Gleason 4+3 or pT3); the definition of disease appearing suitable on MRI for AS was 'any tumour without evidence of T3 disease', however most experts today would argue that any tumour visible on MRI is significant (regardless of whether there is evidence of T3 PCa) [106].
- In a study of 92 men enrolled in AS who underwent T2WI and MRS, the presence or absence of visible PCa on mpMRI was not predictive of outcome [107]. Limitations of the study include use of 'a rising PSA level' as the endpoint for significant PCa (a poor surrogate), a gap of up to 7 yrs between diagnosis and MRI, and poor inter-radiologist correlation.
- One study analysed the incremental benefit of adding T2WI + MRS data to a nomogram for predicting insignificant disease in men with low-risk PCa. A model which added T2WI+MRS significantly out-performed the purely clinic-pathologic model in a 2007 retrospective analysis of 220 men (ROC-AUC = 0.854 vs 0.726, $p < 0.001$, see Figure 2b), but the improved performance of the T2WI-MRS nomogram over the clinic-pathologic

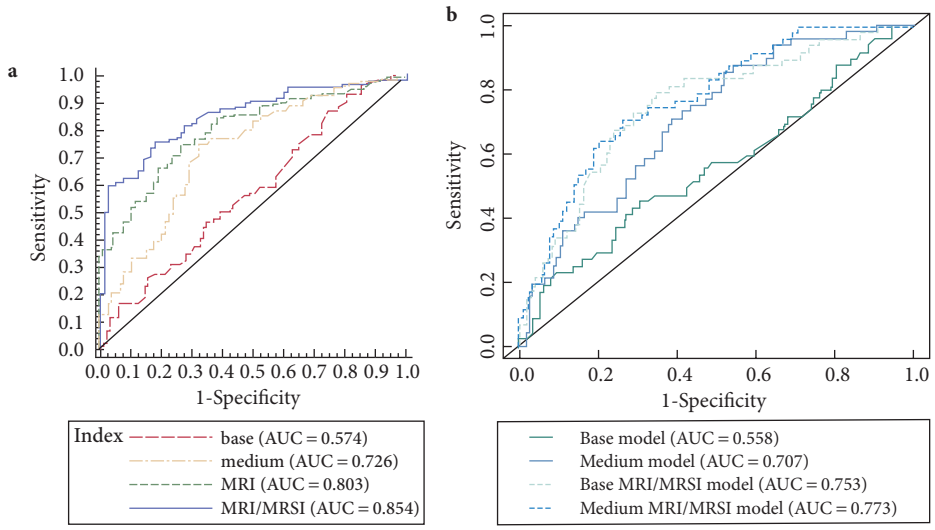



**Fig. 2** Comparison of nomograms to predict insignificant cancer with/without mpMRI data: (a) results of retrospective analysis of 220 men in 2007, (b) results of prospective analysis of 181 men in 2011. (Adapted from Shukla-Dave A et al, BJU Int 2007 and 2012, with permissions from Wiley Blackwell.)

nomogram was marginally non-significant in a more recent, prospective analysis of 181 men (ROC-AUC = 0.773 vs 0.707, p = 0.065; see Figure 2) [108,109].

The balance of evidence suggests a benefit for mpMRI in AS. If active surveillance protocols were revised, MRI would perhaps provide greatest utility if used at diagnosis to guide eligibility and then at 1, 4 and 8 years, which may allow early detection of significant disease and a reduction in surveillance biopsy frequency to 2, 6 and 10 years from diagnosis in men who show no evidence of progression on surveillance MRI, PSA and DRE.

## MRI in T-staging, Treatment Selection and Planning

*Staging* T2WI may be used primary tumour staging (T-staging) for PCa due to its high spatial resolution, which enables detection of extra-prostatic extension (EPE) and seminal vesical invasion (SVI). Subtle signs of EPE used in standardised reporting systems include: extent of contact of the tumour with the capsule, loss of the recto-prostatic angle, bulging or irregularity of the 'pseudo-capsule', reduced signal in the peri-prostatic fat and asymmetry of the neurovascular bundle; these signs can increase the accuracy of MRI in detecting EPE to 77%-80%[110,111]. The main limitation of MRI in T-staging is limited sensitivity, due to its inability to detect microscopic EPE. Adding functional parameters to T2WI may improve this. One study reported that adding DCEI to T2WI for T-staging resulted in a sensitivity of 86% and specificity of 95% for detecting EPE [112]. Another study failed to validate these findings [113], however, and two studies reported that combining MRS and T2WI failed to improve accuracy over T2WI alone in staging [114,115].

The optimal MRI protocol for staging remains unclear, thus the 2012 ESUR guidelines are reasonable [2] in suggesting that a mpMRI specifically for T-staging should include T2WI, DCEI, DWI and an ERC, while MRS is optional, and using 3T may remove the need for an ERC.

*Treatment selection* There are no published trials on the use of MRI to guide treatment choice or viability of radical prostatectomy in high risk PCa. Men classified as having high risk PCa are known to be a highly heterogenous group in terms of surgical resectability and outcomes [116–118], some of whom are curable by radical prostatectomy and others of whom are not curable by surgery and would benefit more from combined androgen deprivation and radiotherapy. It is possible that routine MRI in higher-risk men may identify those with evidence of extensive T3 disease, whom are inappropriate for radical prostatectomy. MRI could be added to existing nomograms for prediction of organ-confined disease in high-risk men [119]. Likewise in intermediate risk PCA, men with evidence of higher volume/ grade disease on MRI may be at higher risk of failure with low dose rate brachytherapy, and those with or extensive EPE or SVI on MRI may be inappropriate for radical prostatectomy [120].

*Surgical planning* Two studies have prospectively trialled the incorporation of MRI into pre-operative plans for nerve-sparing prostatectomy. In one study, 135 men had T2WI with an ERC at 1.5T then the urologist judged need for NVB resection on a scale from 1 (definite preservation) to 5 (definite resection), before and after reviewing the MRI. Histopathology determined that neurovascular bundle (NVB) resection was warranted in 16% of NVBs due to posterolateral ECE or PSMs. ROC-AUCs were significantly better for the post-MRI versus pre-MRI surgical plan (0.83 vs 0.74, $p < 0.01$) [121]. In a similar study, 104 consecutive men with known PCa underwent mpMRI using an ERC at 1.5T prior to Robot-Assisted Radical Prostatectomy (RARP). After review of MRI results, the initial surgical plan was changed in 27% of men (from a non-nerve spare to a nerve spare in 61%, and from a nerve-spare to a non-nerve spare in 39%). There were no PSMs in any of the 61% of men on the side where the plan was changed to a nerve spare based on MRI [122]. These studies support the use of MRI in nerve-sparing decisions. MRI may also be of value in guiding the width of resection for the apical, anterior, posterior and bladder neck dissection: MRI evidence of high grade/ volume tumour or of ECE may prompt a wider dissection in that region, although there are no studies to guide practise in this area.

*Radiotherapy planning* MRI may help define the location, grade, volume and extent of prostate tumours more accurately if used in combination with biopsy, than biopsy alone. This has created great interest in the concept of using MRI for treatment planning in external beam therapy, especially Intensity-Modulated Radio-Therapy (IMRT) [123–125]; an MRI-based boost-dose up to 80 Gy to the dominant tumour appears to be associated with low toxicity, however cancer control outcomes are not yet available [126]. EPE on MRI was shown to be the strongest predictor of biochemical recurrence in one study of men undergoing combined brachytherapy + IMRT, which suggests it could be useful in guiding prognosis and treatment planning [127]. MRI has been used to plan low dose brachytherapy, although using an endorectal coil can distort the prostate and lead to errors in dosimetry planning [128], and the 8-year biochemical recurrence-free survival in one series was poor for both low risk (80%) and intermediate risk (66%) men following MRI-guided focal brachytherapy [129].

*Focal therapy planning* Focal therapy is a minimally invasive therapy for prostate cancer that involves the localisation and ablation of an area/s of significant cancer, whilst sparing the remainder of the prostate, with the aim of minimising treatment related side effects that can have a major impact on quality of life. Medium to long-term outcomes of modern techniques are not yet available [130,131], but short-term outcomes appear favourable for selected men in recent studies

[132], especially those where mpMRI was used together with template mapping biopsy [133]. The key to a successful outcome with focal therapy lies in the accurate localisation and risk stratification of all foci of clinically significant cancer. MRI appears to be of value at all stages of focal therapy, including: localisation and categorisation of risk in all foci, monitoring during treatment to guide the treatment field and monitor for toxicity and efficacy, initial post-treatment imaging to determine success and exclude residual viable disease, and finally follow up imaging for recurrence &/or monitoring of low risk foci. The role of MRI in focal therapy, although promising, remains experimental. Well-designed, prospective trials are urgently needed to guide practice in this emerging area [130].

## Conclusion

Multi-parametric MRI is an emerging modality in the diagnosis, staging, grading and treatment planning of prostate cancer. At this stage, the optimal techniques and indications remain unclear. It should only be interpreted by urologists as one part of the overall clinical assessment and should only be performed by specially trained radiologists using a standardised protocol reporting system.

## Conflict of Interest

None declared.

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